REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-11 and 15-34 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. The limitation "the pharmaceutical formulation has a water content of at least 3%" in new claim 21 is based on page 3, line 3, of the specification.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-11 were rejected under Section 103(a) as allegedly unpatentable over MITRA (US 5,955,105) as evidenced by HANDBOOK (*Handbook of Pharmaceutical Excipients, 5th Ed.*, pp. 134, 725 and 731-732, 2006) and MSDS (Material Safety Data

Sheet, L-Thyroxine, sodium salt) in view of EUROPEAN (*European Pharmacopoeia*, pg. 1438, 2002) and FRANZ et al. (US 2003/0032675). Applicants traverse.

Applicants' claims 1 and 21 are directed to pharmaceutical formulations, which comprise:

(a) an effective amount of levothyroxine sodium,

(b) microcrystalline cellulose having a mean particle size of less than 125 μm and present in an amount of 60 to 85% w/w, and

(c) pregelatinised starch present in an amount of 5 to 30% w/w *which is produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying.*

Additionally, claim 21 requires that the pharmaceutical formulation has a water content of at least 3% w/w. Instead of the definition used in claims 1 and 21, claim 20 defines 'pregelatinised starch' as containing *about 5% free amylase, 15% free amylopectin, and 80% unmodified starch.* None of these pharmaceutical formulations is disclosed by the cited documents (including MITRA).

Initially, it is noted that the Examiner was incorrect in contending at page 4 of the Office Action that Applicants did not address the combination of documents cited in his obviousness rejection and only argued them individually. Instead, Applicants explicitly stated at page 10 of the previous response that "the present claims are not obvious over the cited document**s**" (emphasis added).

MITRA disclosed stabilised pharmaceutical preparations containing levothyroxine sodium. Stabilisation was achieved using a water-soluble glucose polymer (e.g., malto-dextrins at column 4, lines 15-16), and a partially soluble or insoluble cellulose polymer (see claim 1). Example 10 of MITRA used microcrystalline cellulose as the partially soluble or insoluble glucose polymer, and starch as the water-soluble glucose polymer. Contrary to previous assertions by the Examiner, pregelatinised starch as used in Applicants' claimed invention is not synonymous with MITRA's starch. Withdrawal of the Section 102(b) rejection and the Examiner's admission that Applicants' claimed invention is novel appear to concede this issue. Moreover, pregelatinised starch and MITRA's water-soluble starch are not functional equivalents because, despite the Examiner's

assertion at page 4 of the Office Action, there is no teaching or even suggestion in the evidence of record (including FRANZ) that 'pregelatinised starch' and 'starch' are equivalents. Further, there is no reasonable expectation of substituting one for the other in a formulation containing levothyroxine without a change in function.

Both HANDBOOK and EUROPEAN, which were cited by the Examiner, list the entities 'starch, pregelatinised' and 'starch' (unmodified) separately because they are universally recognised in the art as distinct excipients with very different properties and functionalities. It is not possible to merely substitute starch for pregelatinised starch in a pharmaceutical formulation without changing the characteristics of the formulation and, as such, they are not mere functional equivalents.

The requirement of Applicants' claims to include pregelatinised starch provides the claimed formulations with different solubility characteristics as compared to other formulations containing water-soluble, unmodified starch. Additionally, pregelatinised starch has a number of other different chemical and physical properties as compared to unmodified starch. Specifically, pregelatinised starch possesses enhanced flow and compression characteristics as compared to unmodified starch: pregelatinised starch granules occur as irregular chunks or thin plates, whereas unmodified starch occurs as a powder comprising very small spherical or ovoid granules. Thus, in contrast to the Examiner's assertion made to justify the obviousness rejection, 'pregelatinised starch' and 'starch' are clearly not functional equivalents.

Furthermore, the compatibility with lubricants of pregelatinised starch and unmodified starch is different and altering the excipient may require a change in the choice of lubricant. Replacing the starch in the formulation of MITRA's Example 10, which has 0.5% magnesium sterate, with pregelatinised starch would be expected to have a not insubstantial effect on tablet strength and dissolution properties. Thus, the magnesium sterate lubricant may need to be replaced by stearic acid or the level of magnesium sterate reduced to compensate for that change (see HANDBOOK at page 731). Thus, pregelatinised starch is not merely an alternative for unmodified starch having some properties that may be used interchangeably since one of ordinary skill in the art making

the Examiner's proposed substitution would have reasonably expected to make other changes in the formulation (e.g., choice and/or amount lubricant).

The failure of MITRA to disclose the claimed invention was also not remedied by the attempt in this rejection to combine that disclosure with MSDS, EUROPEAN, and FRANZ. Applicants' claims differ from what is disclosed in MITRA in that their invention requires pregelatinised starch instead of unmodified starch. The characteristics of pre-gelatinised starch that distinguish over MITRA's water-soluble glucose polymer (i.e., unmodified starch) were recited in Applicants' claims in the previous response.

Applicants note too that one of ordinary skill in the art would have had no reason to use MITRA's Example 10 as the starting point for modifying a pharmaceutical formulation because neither stability nor dissolution data were provided as reference points to determine improvement. Even if one of ordinary skill in the art were to combine what is disclosed by MITRA's Example 10 and FRANZ's claim 6, there is no evidence provided in the Office Action from which to conclude with a reasonable expectation of success that such a combination would result in Applicants' claimed formulation having the especially advantageous stability and disintegration characteristics as disclosed in their specification (see data and discussion at pages 7-11 under "Conclusions").

Formulations according to the present invention have the surprising (and totally unexpected) property that those with a higher moisture content (4.1 or 4.7%) display higher stability than those with a lower moisture content (2.4 or 2.7%). These results are shown in Table (C) at page 10 of Applicants' specification; the conclusions are summarized at page 7, lines 39-41, of Applicants' specification. For emphasis, new claim 21 requires that the pharmaceutical formulation have a water content of at least 3% w/w.

This characteristic of Applicants' claimed invention is in clear contrast to MITRA's formulations, wherein the latter having a higher moisture content are found to be less stable than those having a lower moisture content. MITRA discloses that for some of the formulations, those with a moisture content of 4.5% are unstable whereas those with a moisture content of 3% are stable (column 4, lines 50-58). MITRA teaches away from the formulations claimed by Applicants because MITRA prefers a moisture content of 0-3%. Therefore, the problem facing one of ordinary skill in the art is that the formulations

disclosed in MITRA must be produced in such a way as to minimize their moisture content in order for them to be stable. This would not have led to Applicants' claimed formulations.

There appears to have been a misunderstanding about Applicants' previous arguments regarding the higher stability of their claimed formulations. Thus, Applicants apologise if that misunderstanding was due to any ambiguity or lack of clarity in the last response. The formulations of their claimed invention have a combination of microcrystalline cellulose and pregelatinised starch, which is partially water soluble, in contrast to the water-soluble glucose polymer (i.e., unmodified starch) used in MITRA's formulations. The combination of microcrystalline cellulose and pregelatinised starch has been found to have the advantageous property of being stable at relatively high moisture content. This characteristic was neither suggested in the prior art of record nor would it have been obvious to one of ordinary skill in the art.

Applicants' invention provides a formulation that remains stable at relatively high water content. In contrast, MITRA teaches that lowering the moisture content is important to obtain a stable formulation, with a preference for a moisture limit of 0 to 3% (see column 4, lines 50-58). But drying a pharmaceutical formulation to obtain low levels of moisture is not straightforward and requires careful handling. This is especially true of a levothyroxine sodium-containing formulation due to the drug's thermal instability, which requires the use of low-temperature drying techniques in MITRA (see column 6, line 66, to column 7, line 5). Applicants' claimed formulations do not require the water content to be reduced to a low level (e.g., less than 3% w/w) to achieve stability. They are surprisingly stable even at higher levels as is demonstrated in Table (C) at page 10 of Applicants' specification. Therefore, it is established that the pregelatinised starch in the claimed invention unexpectedly provides a formulation that does not need to have the water level reduced to 3% w/w or less to achieve an acceptable stability, and that has an advantageous stability at higher moisture levels (e.g., at least up to 6% w/w).

One of ordinary skill in the art starting from MITRA's formulations and modifying them by replacing unmodified starch with pregelatinised starch would not have had a reasonable expectation that this change would have resulted in the surprising (and

totally unexpected) property that the resultant formulations display increasing stability with higher moisture content. As was discussed above, this is a complete reversal of the property of MITRA's formulations that display increasing stability with lower moisture content. Thus, MITRA teaches away from Applicants' invention that achieves stability with a moisture content higher than what was preferred in the cited document. Moreover, there is nothing else in the evidence of record that it would have been obvious to replace the starch in MITRA's formulation with pregelatinised starch to provide an advantageous tolerance to high moisture levels (i.e., water content of at least 3% w/w).

In summary, the cited documents fail to provide any teaching or suggestion as regards a preference among pharmaceutical excipients, nor do they make obvious the modification of the excipients used in prior art formulations. For example, there is nothing in FRANZ that would have made it obvious to one of ordinary skill in the art to replace starch in an existing formulation with pregelatinised starch, nor was there any evidence that such a replacement would lead to an advantage. On the contrary, FRANZ clearly sets out that the formulations to which it relates are within the parameters that are described in MITRA's Example 10 (see paragraph [0026]) and, thus, the changes required by the Examiner's combination would not have been obvious from the cited documents.

In the context of the cited documents as a whole, claim 6 of FRANZ would not be interpreted by one of ordinary skill in the art as teaching that starch in the formulations described in MITRA should or could be replaced with pregelatinised starch. On reading FRANZ, one of ordinary skill in the art seeking guidance concerning the exact composition of a levotroxin-containing formulation would turn to MITRA. Given that MITRA is concerned with advantageous levotroxin-containing formulations, whereas FRANZ is silent on the merits of various pharmaceutical excipients, one of ordinary skill in the art would take MITRA as being authoritative on the excipient blend, as FRANZ acknowledges itself. Therefore, one of ordinary skill in the art would either ignore the nature of the excipients listed in FRANZ's claim 6 or, in the unlikely event they are considered relevant, the ordinarily-skilled artisan would modify FRANZ's formulation to conform to

MITRA's formulation instead of the reverse because FRANZ's claim 6 was outside the parameters set out in MITRA.

Therefore, for all of the above reasons, it is submitted that the present claims are not obvious over the cited documents. Applicants submit that these features of their claimed invention are sufficient to distinguish over the cited documents so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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